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Effect of Passive Heating on Males and Females with Elevated Arterial Stiffness

Forrest Blake Robinson
University of Arkansas, Fayetteville

Effect of Passive Heating on Males and Females with Elevated Arterial Stiffness

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Master of Science in Kinesiology

by

Forrest Blake Robinson
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This thesis is approved for recommendation to the Graduate Council.

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Dr. Matthew Ganio
Thesis Director

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Dr. Michelle Gray
Committee Member

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Dr. Stavros Kavouras
Committee Member

Abstract

Context: Cardiovascular disease (CVD) is one of the leading causes of mortality in the United States, accounting for about 1 in every 4 deaths annually. Studies have shown that passive heating does have some degree of effect on arterial stiffness, but not much is known about populations with higher stiffness. **Objective:** To examine the independent effect of core temperature increase during passive heating on arterial stiffness**. Methods:** Participants visited the lab three times; one familiarization and two experimental trials. The experimental trials consisted of subjects being passively heated in an environment of 40°C / 40% relative humidity (HEAT) or normal laboratory conditions (CONTROL). Participants were 48.9 ± 12.0 years old of age, 66.7± 12.6 kg, 168.2 ±8.8 cm, and 7.7 ± 2.0 m/s central pulse wave velocity. **Main Outcome Measures:** Before and after passive heating, pulse wave velocity (PWV measures occurred via ultrasound at the tibial, radial, femoral and carotid artery sites). At the same time, rectal temperature (T_{rec}) was measured. T_{rec} was measured with rectal thermistors; differences between trials confirm the changes that occurred as a result of environmental conditions. Central arterial stiffness was assessed by using measures between the carotid and femoral artery sites, while peripheral stiffness was assessed using the radial and tibial artery sites. The radial site was used for upper peripheral arterial stiffness and the tibial site was used for lower peripheral arterial stiffness. **Results:** T_{rec} at the end of passive heating showed significant differences between the CONTROL and PASSIVE HEAT trials respectively (36.53 ± .16 vs. 38.14 ± .49°C; $p < 0.001$). There were no interactions ($p>0.05$) between time and condition for central pulse wave velocity (Δ 1.83 ± 50.44 vs. 3.25 ± 67.34 cm/s; for control and passive heating respectively), upper peripheral (Δ 51.50 ± 60.87 vs. 92.77 ± 82.81 cm/s), and lower peripheral pulse wave velocities (Δ 46.99 ± 68.55 vs. 23.70 ± 156.67 cm/s). **Conclusions:** The findings of this study indicate that differences in mean body temperature do not result in significant decreases in arterial stiffness following passive heating in individuals with poor arterial stiffness at baseline.

Acknowledgements

The authors would like to thank all of the subjects for their time and participation in making this project possible. The authors would like to thank Ben Harris, Andrew Schween, and Haley Reynebeau for their contributions to this study.

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Introduction

Cardiovascular disease is among the leading killers in the United States causing close to 600,000 deaths per year, which comes out to about 1 in 4 deaths (CDC, 2015). This disease is extremely costly in regards to medical expenses and insurance costs, and those costs are estimated at 109 billion dollars each year (CDC, 2015). High blood pressure (i.e., hypertension), high LDL cholesterol, and smoking are three of the primary risk factors in regards for cardiovascular disease, and around half of Americans (49%) have at least one of these risk factors (CDC, 2015). Hypertension is one of the more costly risk factors of cardiovascular disease, and it is often preceded by increased arterial stiffness (O'Rourke. 1990). For example, when rats received a high fat / high-sucrose diet (HFHS) they developed an increase in arterial stiffness that preceded hypertension by 5 months (Weisbrod et al. 2013). Therefore, as a precursor to hypertension, arterial stiffness may be a more precise indicator of arterial health, and evidence suggest that it can more accurately predict cardiac events than blood pressure alone (Duprez et al. 2007).

There have been many solutions for hypertension and arterial stiffness, one of which is exercise. The cardiovascular response to exercise has been well documented to decrease the risk of cardiovascular disease through decreased arterial stiffness (Manson et al.1999). As an individual exercises the blood vessels throughout the body undergo vasodilation and this allows greater blood flow to the muscles. Exercise has been shown to decrease both leg and central arterial stiffness in acute bouts of exercise (Kingwell et al. 1997). One of the hormones that control the vasodilation response is nitric oxide. Nitric oxide has also been seen to play a major role in arterial compliance (Bellien et al. 2010). With these findings it is reasonable to conclude that exercise causes the release of nitric oxide and therefore increases arterial compliance.

Although physical activity is very effective for decreasing arterial stiffness, it may not always be possible because of health risk factors or mobility impairments. Therefore alternatives to exercise should be investigated. Another mode of decreasing arterial stiffness is through passive heat stress. Preliminary studies conducted by our laboratory have looked examined the effect of passive heat stress on arterial stiffness and provide several justifications for the current study (Ganio et al. 2011; Moyen et al. 2013). In the first study healthy individuals were passively heated to 1.5°C increase in core temperature. Arterial

stiffness was measured with pulse-wave velocity at 0.5,1.0, and 1.5°C above baseline core temperature. As a group, average central and peripheral arterial stiffness did not change from baseline during the protocol, but correlation analysis showed that individual changes in both central and peripheral pulse-wave velocity were dependent on baseline stiffness (Ganio et al. 2011). It was found that individuals with the highest baseline stiffness showed the greatest decrease in arterial stiffness. (Ganio et al. 2011). A follow-up study confirmed this relationship in smokers, such that independent of smoking status, individuals with higher baseline stiffness had the greatest decreases in stiffness when heated (Moyen et al. 2013). These studies imply that passive heating may only be effecting in reducing arterial stiffness in individuals with poor stiffness. Therefore future studies should perform baseline stiffness screening when using passive heating.

This study examined the effects of passive heating on arterial compliance in men and women ranging from 35-60 years old who have been screened and selected for enrollment due to "poor" stiffness. The data from the previous studies in our lab indicate that individuals with poor stiffness respond more drastically to being passively heated (Ganio et al. 2011; Moyen 2013). With this in mind it seems pertinent that a study be conducted on a population of people that have been screened for poor stiffness to see the extent of their response to passive heating. Also, we will only be including postmenopausal women. The basis for these exclusion criteria is results that indicated that menopause augments the age-related increase in arterial stiffness and that endothelial function in women during their menstrual cycle is highly varied (Zaydun et al. 2006; Williams, 2001).

The purpose of this study was to examine the effect of passive heating on reducing arterial stiffness. This study will test the hypothesis that passive heating will decrease arterial stiffness in men and women 35-60 years old who have poor baseline arterial stiffness.

Methodology

Participants were 5 men and 4 women ranging from 35-65 years of age, who had no medical illness, and are not currently on drugs that affect fluid balance. They abstained from alcohol and caffeine on lead-in and testing days, and had a body mass index of 23.40 ± 2.95 kg/m^2. Participants reported to the Human Performance Laboratory (HPL) in the Department of Health, Human Performance and

Recreation at the University of Arkansas for all testing. Prior to enrolling, participants signed an institutionally approved Informed Consent document that abides by the Declaration of Helsinki.

For familiarization, participants reported to the Human performance lab (HPL) and were walked through the informed consent document and the study procedures in detail. During the same visit, participants completed medical history and physical activity questionnaires. Measures of arterial stiffness via Doppler ultrasound (see below) were then taken. Only those with an arterial stiffness that was measured at 6 meters per second or greater were included in the study (Ganio et al. 2011). All participants had their body composition measured using Dual Energy X-Ray Absorptiometry (DXA).

For participants that qualified based off the criteria above, they then performed an exercise test to determine maximal oxygen consumption (VO_2 max). This was performed on an electronically braked cycle ergometer (Racermate Veletron, Seattle, WA) with nose clips attached while breathing in room air and exhaling into a mouthpiece connected to a metabolic cart (Parvo Medics' TrueOne® 2400, Sandy, UT). Exercise started at ~50 watts (W) and increased 25 W every 2 minutes until volitional exhaustion. Every 2 minutes and at exhaustion, heart rate (HR) and rating of perceived exertion was measured.

Participants then took part in separate trials (passive heating, and control [no heating]) that took place in a randomized order separated by a minimum of 72 hours. Participants refrained from alcohol and exercise 24 h, caffeine 12 h, and food 4 h before each trial. Pre-test compliance was verified with a 24-hour history questionnaire. Prior to each visit, fluid intake was encouraged by having participants consume an additional 500 mL (~16 oz) of water the night before testing and 2-3 hours prior to arrival.

The passive heating protocol was as follows. Body mass was measured and a urine sample was provided and used to determine hydration status. During this time, participants were asked to insert a thermocouple 16 cm beyond the anal sphincter in a private bathroom for measurement of core body temperature (Trec).

. Participants were then instrumented with an automated sphygmomanometer (Tango+; SunTech Medical, Inc., Morrisville, NC, USA) for Heart rate (HR), Blood pressure (BP), and for skin temperature (Tsk) (iButtons, Maxim Integrated, San Jose, CA). Participants were then dressed in a water-perfused, tube-lined suit that covered the entire body, except the head, face, hands, and feet (Allen-Vanguard Technologies). The suit permitted the control of skin and core temperature by changing the temperature

of the water perfusing the suit. Participants laid in a supine position on a padded table for approximately 15 minutes prior to baseline measures of arterial stiffness by Doppler ultrasound.

After this resting period, participants were then exposed to passive heat stress (Passive Heating) trial by perfusing warm water (49°C; experimental trial) or room temperature water (34°C; control trial) through the suit. During this time, measures of VO_2, HR, and BP were recorded. Measurements of Trec were continuously recorded during the trial via rectal thermocouple (RET-1, Physitemp, Clinton, NJ) and Tsk data were continuously collected during the trial then downloading after the trial via the skin temperature probes (iButtons, Maxim Integrated, San Jose, CA). Mean body temperature was calculated from the Burton formula (.64rectal + .36skin). For the experimental trial, heating continued until a 1.25°C elevation in rectal temperature was achieved (experimental trial; ~1:00 h). For the control trial, participants laid down for ~50 minutes. Participants remained in the supine position and were allowed to cool off (Passive Heating) by removing the water perfused suit (Allen-Vanguard Technologies) and moving them from the environmental chamber, which was kept at 40°C and 40% humidity throughout the trial, back to the lab conditions baseline was recorded in and, or lie for another hour (control). Measures of arterial stiffness were taken immediately post heating and every 15 minutes for 60 minutes using Doppler ultrasound. During this time, measures of VO_2, HR, Trec, Tsk, and BP were also recorded. Following completion of these measures, participants then voided their bladder into a collection container and a nude body mass measure was obtained, and the thermocouple was then removed in a private bathroom.

Statistical analysis: A two-way repeated measures analysis of variance (ANOVA) with appropriate follow-up tests was used to examine differences in arterial stiffness between experimental condition and time (condition x time). Alpha will be set at 0.05. When Mauchy's test of sphericity was violated the Greenhouse-Geiser correction was utilized. If there was a significant interaction a pair-wise comparison with a Bonferroni correction was used.

Results

Participants included five male subjects and four female subjects. Subjects were individuals who were 48.9 $\pm$ 12.0 years of age, 66.7$\pm$ 12.6 kg, 168.2 $\pm$8.8 cm, a VO_2 max of 34.6 $\pm$ 10.34 ml/kg/min, and 7.7 $\pm$ 2.0 m/s central pulse wave velocity

Heart rate was significantly increased (Figure 1) in comparison to control at immediate post heating ($p = 0.003$); control and passive heating respectively, 15 min post heating ($p = 0.014$), 30 minutes post heating ($p < 0.001$), and 45 minutes post heating ($p = 0.017$). VO_2 was significantly increased at baseline for both trials $3.20 \pm .81$ vs. $2.55 \pm .42$ ml/kg/min; for control and passive heating, respectively, ($p = 0.049$) and 50 minutes into passive heating $3.46 \pm .78$ vs. $2.64 \pm .63$ ml/kg/min; for control and passive heating, respectively, ($p = 0.001$).

Mean arterial pressure was only significantly decreased (Figure 2) in comparison to control at immediate post heating ($p = 0.020$) and 15 minutes post heating ($p = 0.022$). Rectal temperature was significantly higher (Figure 3) at each time point after the initial baseline measure: immediate post heating ($p < 0.001$), 15 minutes post heating ($p <0.001$), 30 minutes post heating ($p < 0.001$), 45 minutes post heating ($p < 0.001$), and 60 minutes post heating ($p < 0.001$). Mean skin temperature was significantly higher (Figure 4) at immediate post heating ($p < 0.001$), and 15 minutes post heating ($p < 0.001$). Mean body temperature was significantly higher (Figure 5) at each time point after the initial baseline measure: immediate post heating ($p < 0.001$), 15 minutes post heating ($p < 0.001$), 30 minutes post heating ($p < 0.001$), 45 minutes post heating ($p = 0.005$), and 60 minutes post heating ($p = .031$).

There was no significant interaction between condition and time ($p>0.05$) for any measures of arterial stiffness (Figures 6-8) indicating no effect of passive heating on central or peripheral stiffness. There was no main effect of time or condition ($p > 0.05$) on lower or central pulse wave velocity. However, there was a main effect of condition on upper peripheral pulse wave velocity ($p = 0.015$). Further, there was a main effect of time on upper peripheral pulse wave velocity ($p < 0.001$); pairwise comparisons revealed significant decrease in pulse wave velocity for immediate post measurement (728.83 ± 25.88 vs. 656.7 ± 23.49 cm/s; for baseline and immediate post, respectively, $p = 0.028$).

Three Pearson product-moment correlations were run to determine the relationship between normothermic baseline pulse wave velocity and changes in pulse wave velocity. There was a moderate, negative correlation between normorthermic baseline central pulse wave velocity and the changes in central pulse wave velocity ($r=-0.51$, $p< 0.001$). There was a moderate, positive correlation between normothermic baseline peripheral pulse wave velocity for both upper peripheral ($r= 0.43$, $p= 0.003$), and lower peripheral ($r= 0.47$, $p= 0.001$).

Discussion

Previous studies have indicated that there may be a significant change in arterial stiffness with passive heating in individuals that have a higher than average baseline (i.e., normothermic) arterial stiffness (Moyen et al. 2013). The purpose of this study was to examine the effect of passive heating on reducing arterial stiffness. This study tested the hypothesis that passive heating will decrease arterial stiffness in men and women 35-60 years old who were screened for poor baseline arterial stiffness. The main finding of this study was that with increases in rectal temperature up to 1.25°C there was a no significant change in average central, upper peripheral, or lower peripheral pulse wave velocity.

It is hypothesized that arterial stiffness has two mechanisms “active” mechanisms and “passive” mechanisms. Nichols et al. 2011 discusses how the active mechanisms are associated with cellular and molecular processes and passive mechanisms correlate more with mechanical stress and hemodynamics. As individuals are passively heated they experience hypotension and that is associated with “sympatholytic-like” substances release around the blood vessels that limit the ability for tissues to vasoconstrict (Crandall et al. 2014). Wilson et al. 2002 found that the amount of cutaneous vasoconstriction was attenuated in individuals who were heat stressed. This response is thought to be assisted by a nitric oxide regulated mechanism.

Another potential mechanism for arterial stiffness changes in the effect of shear stress on the vessels. Shear stress is defined as a strain in the structure of a substance produced by pressure, when its layers are laterally shifted in relation to each other. Lu and Ghassan (2011) state that there is a dynamic balance between mechanical or chemical stimulus and biological repose to these. If a mechanical stimulus is too high, this can lead to either physiological adaptations or a diseased state (Lu and Ghassan 2011). For example exercise would be a physiological perturbation, whereas hypertension would be a pathologic perturbation. These different types of perturbation alter the way blood vessels stretch and effectively change the stiffness of the artery. This mechanism relates to this study because if passive heating can decrease the individuals arterial stiffness, then the amount of sheer stress on the vessel will be habitually decreased and thus preventing the diseased state.

There were no significant differences in central or peripheral pulse wave velocity data. Ganio et al. 2011 discusses the possibility that a higher basal tone could increase individual’s ability to change with

passive heating. This study included individuals who were higher in baseline stiffness, but since no significant changes were observed it could point to baseline stiffness not being a factor or the baseline stiffness simply wasn't high enough to elicit a significant change. Another possibility is that in the previous studies (Ganio et al. 2011; Moyen et al. 2013) individuals were heated to an increase of 1.5°C from baseline.

When considering upper peripheral pulse wave velocity there was a main effect of time. However, when considering each condition individually there was no significant change in pulse wave velocity. A training study conducted by Maeda et al. 2008 saw that after a single acute bout of exercise, systemic arterial stiffness at rest was not affected. Further, this study found that after a 6-month moderate exercise protocol systemic arterial stiffness was significantly decreased immediately post exercise. This indicates that arterial stiffness may be a training adaptation and could explain why an acute bout of passive heating was not enough the significantly affect arterial stiffness.

In previous studies the pulse wave velocity measure were taken during the passive heating protocol. Uniquely this study took measures for an hour post heating. The differences in measurement time points could point to the inconsistency with the results found versus the current body of literature. The participants were removed from the environmental chamber and the water perfused suit was removed immediately following core temperature reaching 1.25°C. For the following hour post-perturbation the participants laid in normal lab conditions, which were significantly colder than the experimental condition. Mechanistically the blood flow would shift from the periphery to more central to counter act the colder environment and there would be vasoconstriction of the vessels. The drastic change in external temperature could have affected the stiffness of the arteries.

Limitations

One possible limitation of this study was that the foot of the pulse wave was identified visually (versus computer aided) when doing analysis. To account for this, analysis of pulse wave information was done by only the three primary researchers. Once analysis of an individual trial was started it was finished by the same researcher to maintain consistency. Further, in this study an ultrasound was used to measure pulse wave velocity whereas previous research has utilized tonometry. Taking pulse wave measures from ultrasound have been found to be comparable to those taken from tonometry (Jiang, Liu,

et. al., 2008). Another possible limitation is that the distance for each individual measurement could have varied slightly, which could have caused some of the high variability in the pulse wave velocity.

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Figure Legend

Figure 1. Effect of passive heat stress on Heart Rate. Significance, between conditions, is denoted by (*) ($p \leq 0.05$).

Figure 2. Effect of passive heat stress on Mean Arterial Pressure. Significance, between conditions, is denoted by (*) ($p \leq 0.05$).

Figure 3. Effect of passive heat stress on Rectal Temperature. Significance, between conditions, is denoted by (*) ($p \leq 0.05$).

Figure 4. Effect of passive heat stress on Mean Skin Temperature. Significance, between conditions, is denoted by (*) ($p \leq 0.05$).

Figure 5. Effect of passive heat stress on Mean Body Temperature. Significance, between conditions, is denoted by (*) ($p \leq 0.05$).

Figure 6. Effect of passive heat stress on central (carotid and femoral) arterial stiffness. Significance, between conditions, differences are denoted by (*) ($p \leq 0.05$).

Figure 7. Effect of passive heat stress on upper peripheral (carotid and radial sites) arterial stiffness. Significance, between conditions, differences are denoted by (*) ($p \leq 0.05$).

Figure 8. Effect of passive heat stress on lower peripheral (femoral and tibial) arterial stiffness. Significance, between conditions, differences are denoted by (*) ($p \leq 0.05$).

Figures

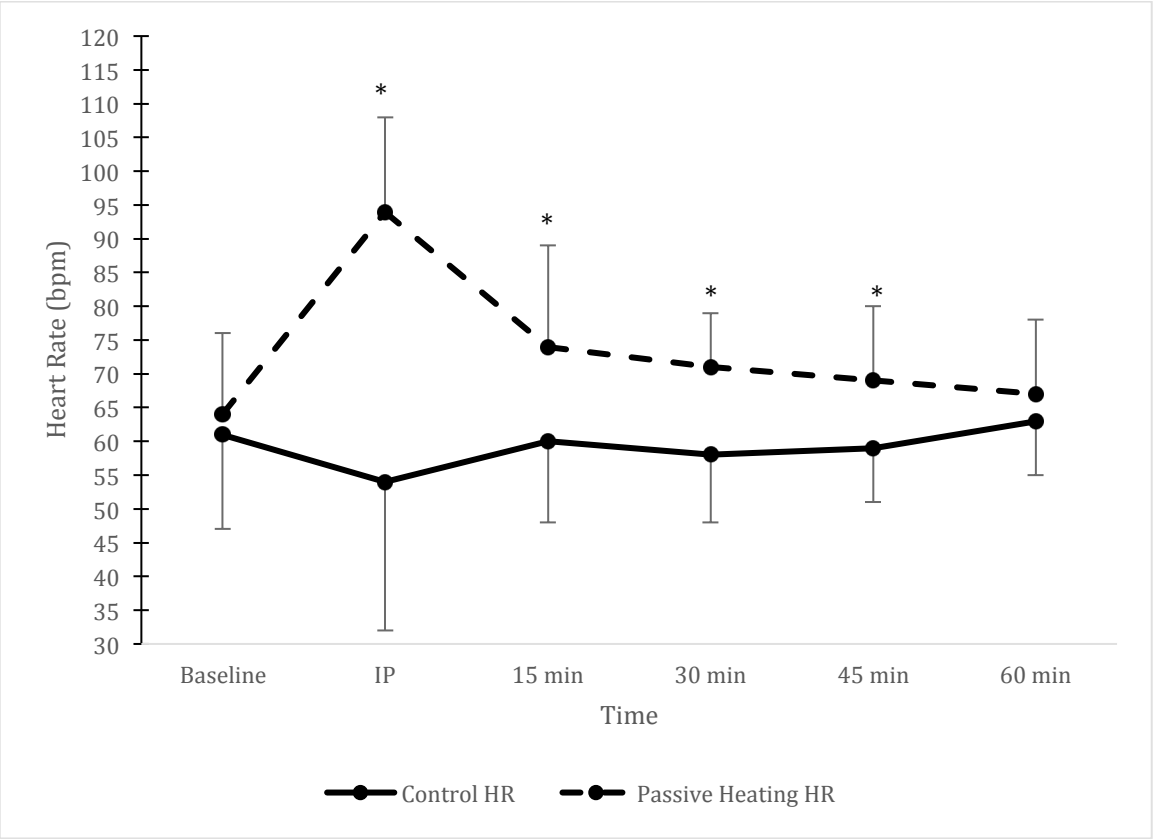
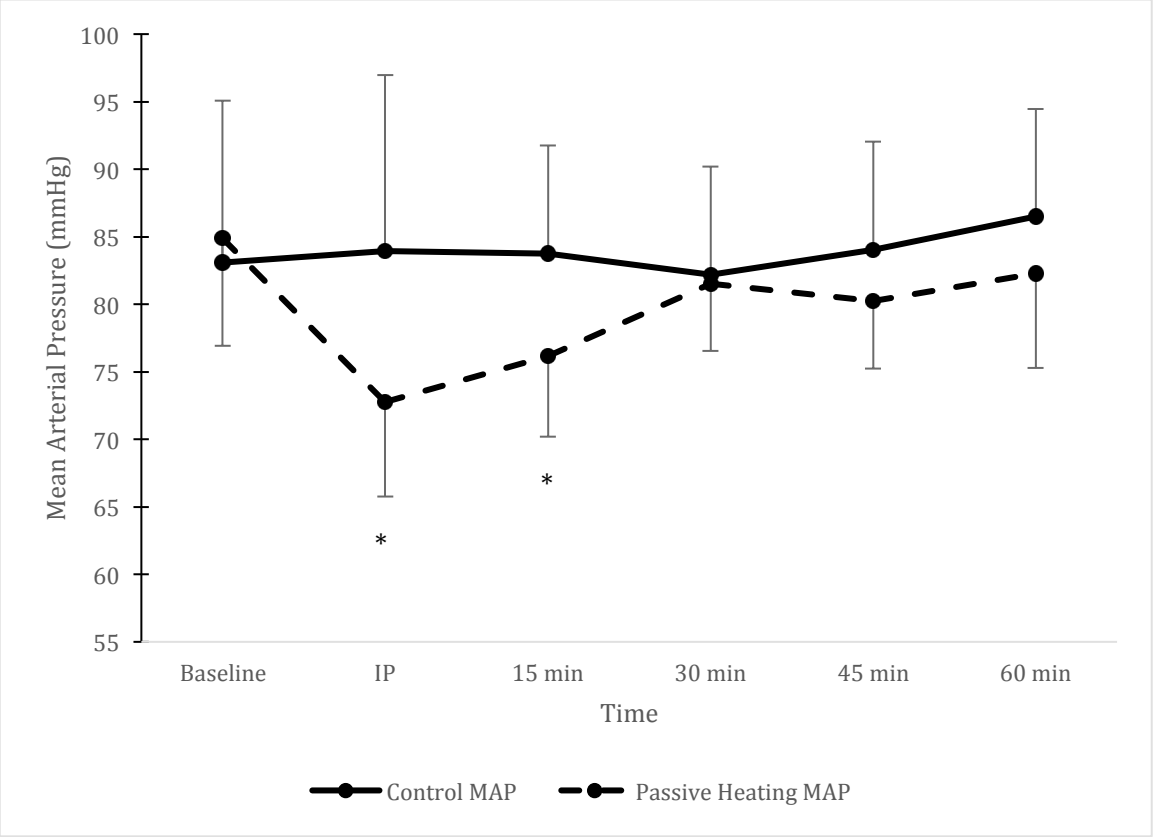


Figure 1. Effect of passive heat stress on Heart Rate. Significance, between conditions, is denoted by (*) ($p \leq 0.05$).



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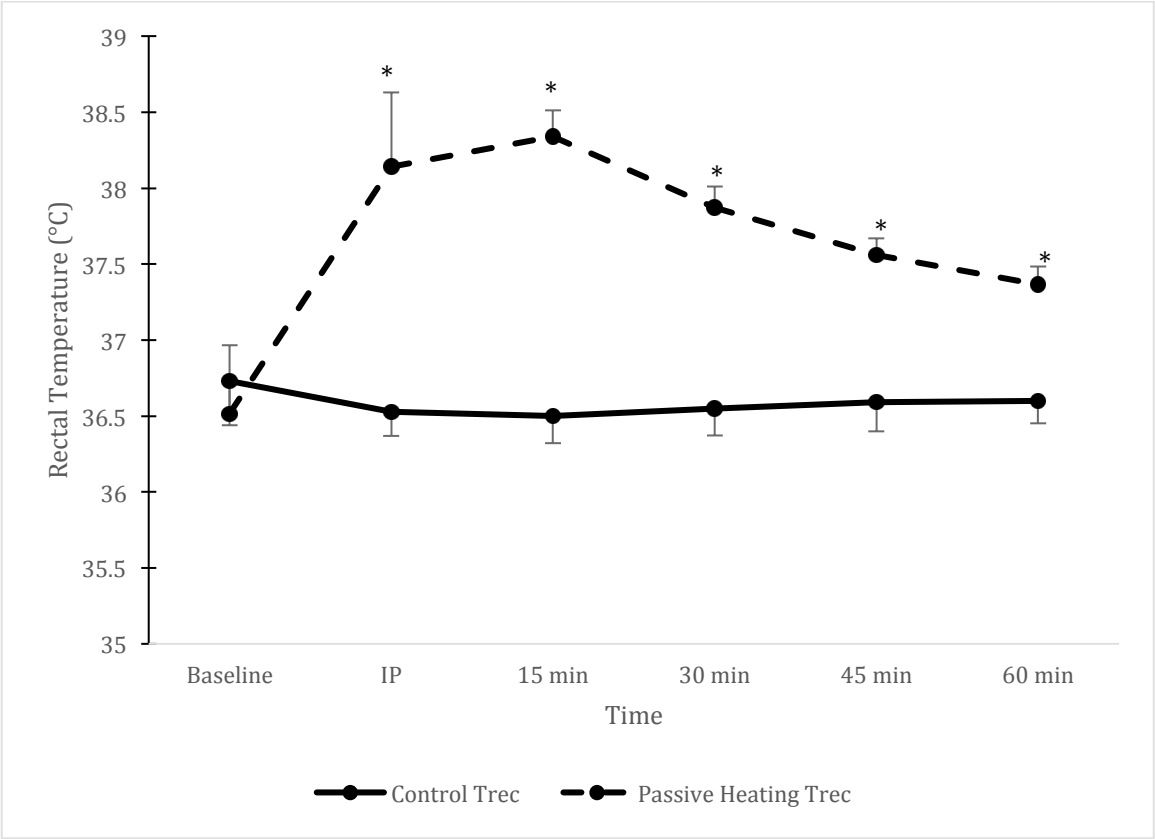

Figure 3. Effect of passive heat stress on Rectal Temperature. Significance, between conditions, is denoted by (*) ($p \leq 0.05$).

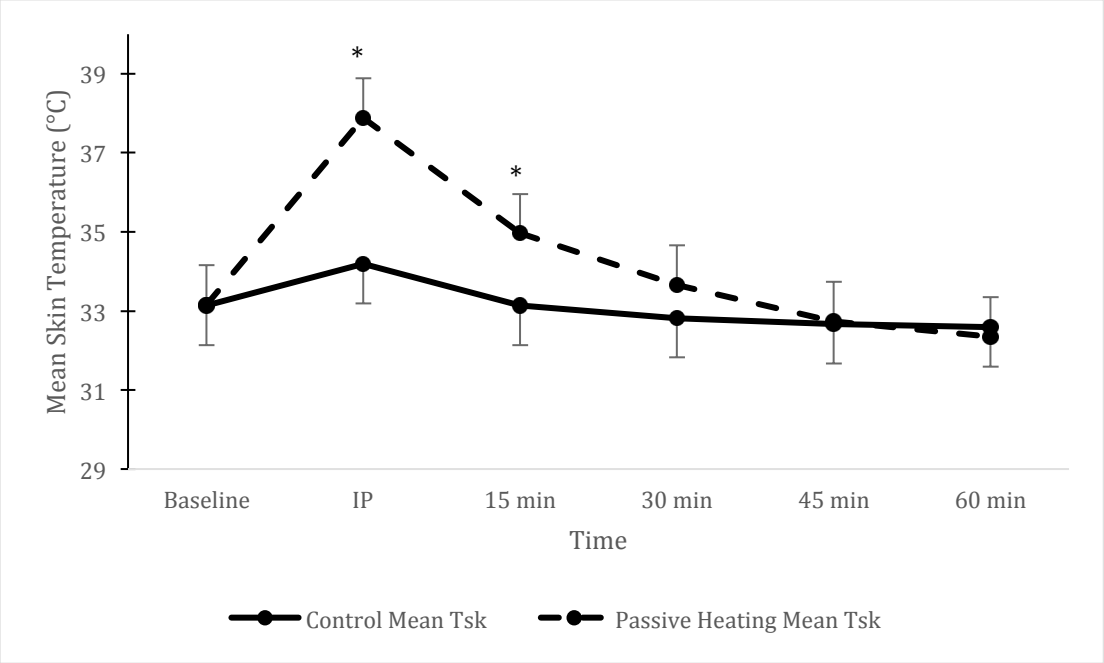

Figure 4. Effect of passive heat stress on Mean Skin Temperature. Significance, between conditions, is denoted by (*) ($p \leq 0.05$).

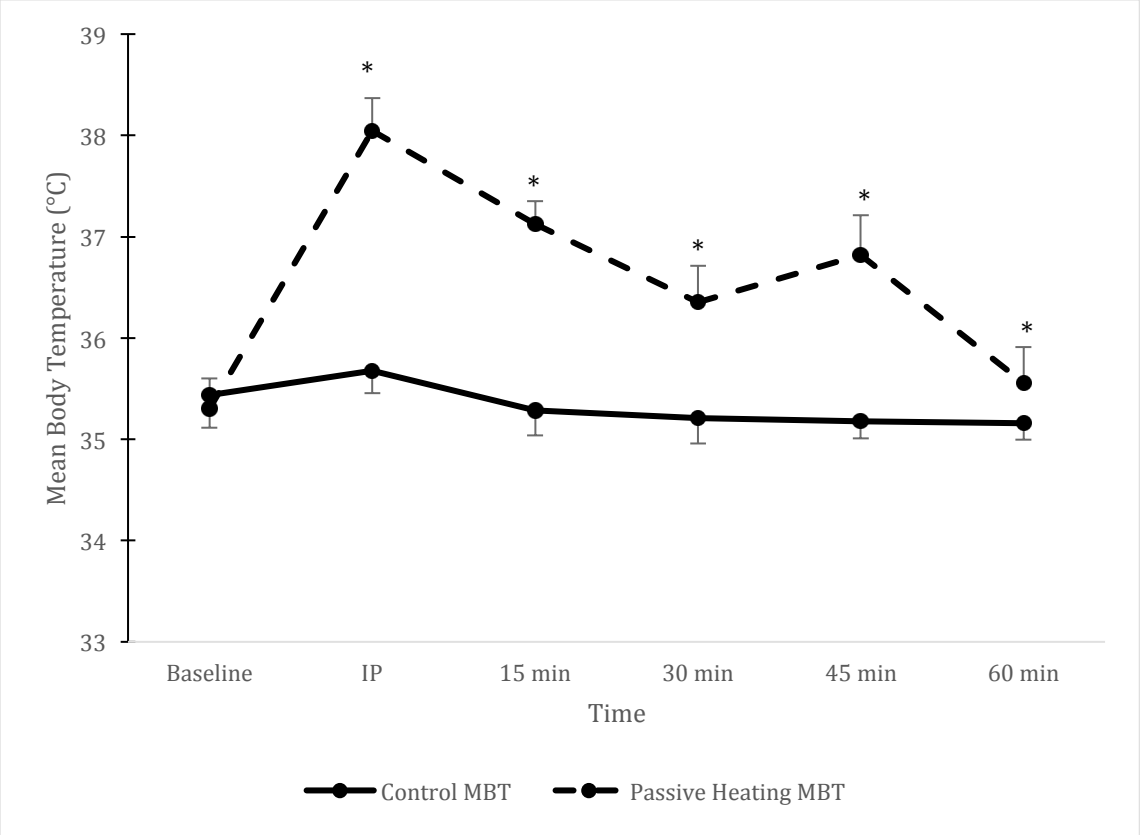

Figure 5. Effect of passive heat stress on Mean Body Temperature. Significance, between conditions, is denoted by (*) ($p \leq 0.05$).

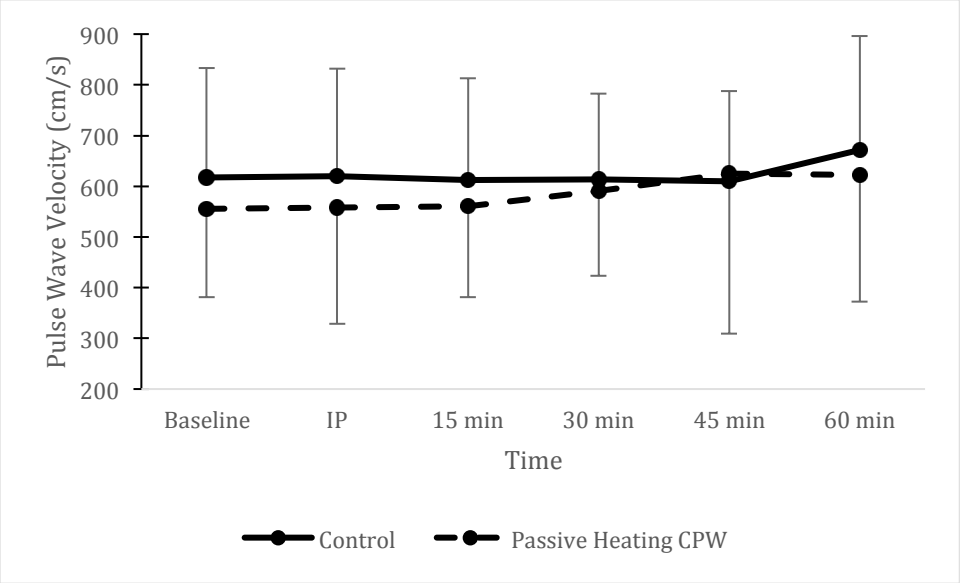

Figure 6. Effect of passive heat stress on central (carotid and femoral) arterial stiffness. Significance, between conditions, differences are denoted by (*) ($p \leq 0.05$).

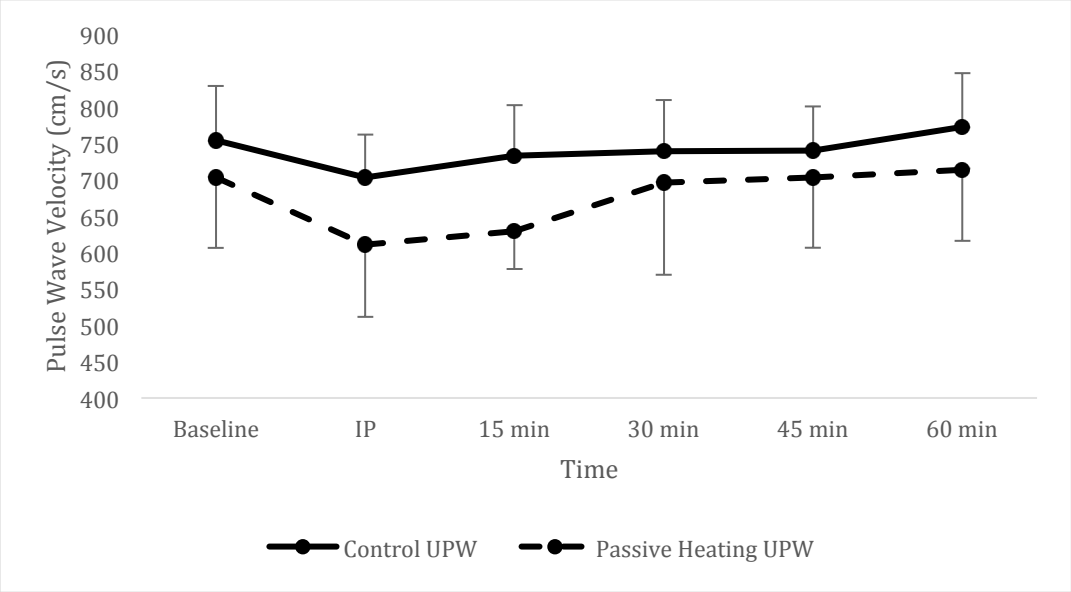

Figure 7. Effect of passive heat stress on upper peripheral (carotid and radial sites) arterial stiffness. Significance, between conditions, differences are denoted by (*) ($p \leq 0.05$).

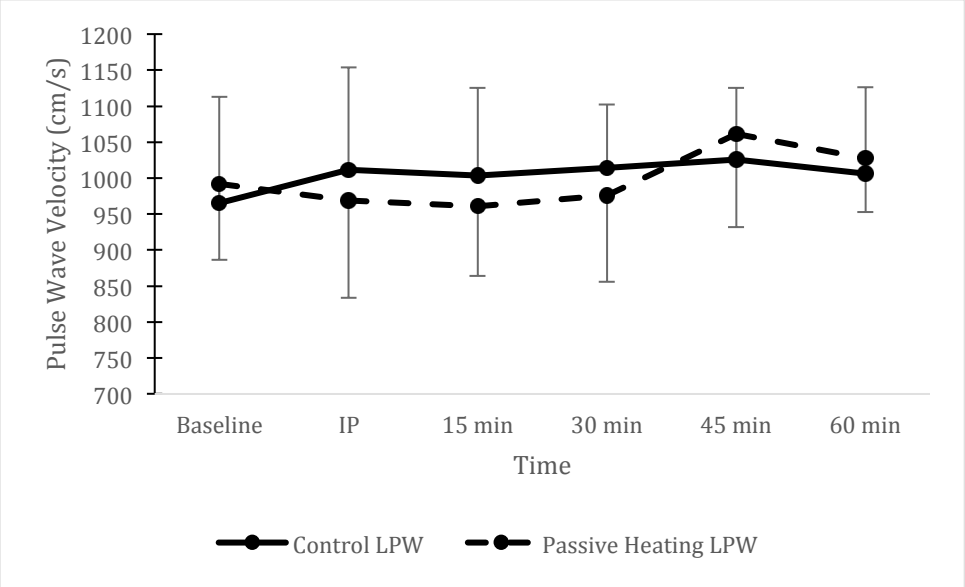

Figure 8. Effect of passive heat stress on lower peripheral (femoral and tibial) arterial stiffness. Significance, between conditions, differences are denoted by (*) ($p \leq 0.05$).

UNIVERSITY OF ARKANSAS

Office of Research Compliance
Institutional Review Board

November 10, 2015

MEMORANDUM

TO:	Aaron Caldwell	Forrest Robinson
	Cash Arcement	Monty Matthew
	Monica Ziebart	Miriah Hadley
	Karly Glass	Haley Reynebeau
	Matthew Tucker	Matthew Ganio
FROM:	Ro Windwalker IRB Coordinator	
RE:	New Protocol Approval	
IRB Protocol #:	15-11-277	
Protocol Title:	*Effects of Heat and Exercise on Arterial Stiffness*	
Review Type:	☐ EXEMPT ☐ EXPEDITED ☒ FULL IRB	
Approved Project Period:	Start Date: 11/09/2015 Expiration Date: 11/08/2016	

Your protocol has been approved by the IRB. Protocols are approved for a maximum period of one year. If you wish to continue the project past the approved project period (see above), you must submit a request, using the form *Continuing Review for IRB Approved Projects*, prior to the expiration date. This form is available from the IRB Coordinator or on the Research Compliance website (https://vpred.uark.edu/units/rscp/index.php). As a courtesy, you will be sent a reminder two months in advance of that date. However, failure to receive a reminder does not negate your obligation to make the request in sufficient time for review and approval. Federal regulations prohibit retroactive approval of continuation. Failure to receive approval to continue the project prior to the expiration date will result in Termination of the protocol approval. The IRB Coordinator can give you guidance on submission times.

This protocol has been approved for 60 participants. If you wish to make *any* modifications in the approved protocol, including enrolling more than this number, you must seek approval *prior to* implementing those changes. All modifications should be requested in writing (email is acceptable) and must provide sufficient detail to assess the impact of the change.

If you have questions or need any assistance from the IRB, please contact me at 109 MLKG Building, 5-2208, or irb@uark.edu.